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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668H AJB

SEPARATE STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NON-INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

DATE: November 13, 2001
TIME: 10:30 a.m.
DEPT.: Court Room 1

HONORABLE MARILYN L. HUFF

Plaintiff Gen-Probe Incorporated respectfully submits the following statement of undisputed material facts, together with references to supporting evidence, in support of its motion for partial summary judgment of non-infringement under the doctrine of equivalents.

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UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
1. Vysis has previously admitted that TMA is a sequence-specific amplification method and does not use methods of non-specific amplification.	Defendant's May 25, 2001 Statement of Disputed Facts In Opposition to Plaintiff's Motion for Partial Summary Judgment, Facts No. 26-28.
2. All of the claims of the '338 patent incorporate an "amplification" element. The Court's June 20th Order confirms that each of those claims and incorporated amplification elements literally encompasses *only* non-specific amplification techniques.	June 20, 2001 Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 patent, claim construction of the term "Amplifying" as found in the '338 patent at 11:5-6.
3. The differences between specific amplification methods and non-specific amplification methods are substantial.	(Mullis Decl., ¶ 7.)
4. The methods do not perform the same function in the same way to achieve the same result.	(Mullis Decl., ¶ 7.)
5. Gen-Probe's TMA method functions to exponentially increase both the ***absolute*** and ***relative*** amount of a particular nucleic acid sequence of interest in a mixture of nucleic acids.	(Mullis Decl., ¶ 18.)
6. In direct contrast, non-specific amplification functions only to increase the absolute amount of *all* nucleic acids present in a sample and does ***not*** increase the relative amount of a particular	(Mullis Decl., ¶ 18.)

UNDISPUTED MATERIAL FACTS	SUPPORTING EVIDENCE
nucleic acid sequence of interest.	
7. Vysis' own expert has admitted the differences in function between specific amplification and non-specific amplification. [N]on-specific amplification techniques amplify all of the nucleic acid in a sample, both target and non-target nucleic acid. Specific amplification techniques, ***in contrast***, are intended to amplify only the target nucleic acid.	May 25, 2001 Declaration of David H. Persing, M.D., Ph.D. submitted in opposition to Gen-Probe's April 30, 2001 Motion for Partial Summary Judgment ("Persing Declaration") at page 5, lines 3-6 (emphasis added).
8. When a particular nucleic acid sequence of interest is contained in a mixture of nucleic acids in a clinical sample, TMA enables a person skilled in the art to exponentially copy the sequence of interest.	(Mullis Decl., ¶ 19-22.)
9. This makes it easy to determine whether or not a pathogenic microorganism is hiding among millions of other organisms in a patient sample.	(Mullis Decl., ¶ 22.)
10. Specific amplification is useful for diagnostic purposes even without a target capture step. In contrast, non-specific amplification is *not* a viable diagnostic method because it does not increase the amount of a target nucleic acid relative to everything else. Vysis' own expert witness has admitted this important distinction:	Persing Declaration at page 5 lines 1-6 (emphasis added).

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
Without the use of target capture prior to amplification, ***non-specific amplification would not be a viable technique for detecting target nucleic acids in a sample*** because, as pointed out in the quoted paragraph, non-specific amplification causes the replication of virtually any nucleic acid sequence, including other irrelevant nucleic acids in the sample.	
11. Therefore, Dr. Persing has admitted that "without the invention [i.e., the combination of a preliminary "target capture" step with amplification], ***only specific amplification could be used***."	Persing Declaration at page 5 lines 13-14 (emphasis added).
12. The enzymes and primers used in any amplification process can be specific or non-specific.	(Mullis Decl., ¶ 28.)
13. The primers used in Gen-Probe's specific TMA amplification method have been carefully selected by Gen-Probe's scientists and are generally designed to bind to specific, unique sequences in a DNA or RNA molecule.	(Mullis Decl., ¶ 34-36; Longiaru Decl., ¶ 6.)[1]
14. In amplification processes, sequence-specific primers and enzymes such as those used in TMA play a role substantially different	(Mullis Decl., ¶ 32.)

[1] All references to the "Longiaru Decl." Refer to the Declaration of Dr. Matthew Longiaru that was submitted on April 30, 2001 in support of Gen-Probe's earlier Motion for Partial Summary Judgment. A true and correct copy of the Longiaru Declaration is attached as Exhibit 1 to the Notice of Lodgment of Exhibits filed concurrently herewith.

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
from non-specific primers and enzymes.	
15. This fact is well known to those of ordinary skill in the art.	(Mullis Decl., ¶ 32.)
16. For example, specific primers and enzymes can function together to amplify a target nucleic acid only if the specific sequence of interest bound by the primer and/or recognized by the enzyme is present in the sample.	(Mullis Decl., ¶ 32.)
17. By contrast, non-specific primers and enzymes will amplify *any* and *all* sequences present in the sample.	(Mullis Decl., ¶ 33.)
18. The random primers will bind to all of the sequences in the sample and non-specific replication enzymes will catalyze DNA synthesis at points throughout the entire lengths of the nucleic acid molecules present without regard to sequence.	(Mullis Decl., ¶ 33.)
19. In its TMA method, Gen-Probe uses two amplification enzymes that depend upon the presence of specific primers.	(Longiaru Decl., ¶ 6-7; Mullis Decl., ¶ 34.)
20. One of these enzymes is reverse transcriptase ("RT").	(Longiaru Decl., ¶ 7; Mullis Decl., ¶ 35.)
21. RT is a DNA polymerase that produces a complementary DNA strand copy of a single-stranded RNA or DNA that has a bound primer.	(Longiaru Decl., ¶ 7; Mullis Decl., ¶ 35.)
22. In TMA, RT produces complementary DNA	(Longiaru Decl., ¶ 7; Mullis Decl., ¶ 35.)

UNDISPUTED MATERIAL FACTS	SUPPORTING EVIDENCE
from the target nucleic acids (or their complementary strands) only if the sequence-specific primers first bind to a single strand of RNA or DNA.	
23. If the target organism is not present in the sample, the primers will be unable to bind to the captured sequence and the RT will not initiate synthesis.	(Longiaru Decl., ¶ 7; Mullis Decl., ¶ 35.)
24. Another specific primer used in Gen-Probe's method also includes a specific "promoter" sequence that is recognized by another enzyme ("T7 RNA polymerase") that binds specifically to that promoter sequence to produce many RNA copies by transcription.	(Longiaru Decl., ¶ 9; Mullis Decl., ¶ 35.)
25. A functional "T7 promoter" is formed in the course of the TMA process if, and only if, (1) the primer finds and binds to its complementary target sequence in the captured target molecule so that the target sequence is copied by reverse transcriptase and (2) the second primer binds to the newly synthesized DNA and DNA polymerase makes the complementary DNA strand.	(Longiaru Decl., ¶ 9; Mullis Decl., ¶ 35.)
26. If this double-stranded, and hence functional, T7 promoter *is* formed as a result of these *two* primer binding and extension	(Longiaru Decl., ¶ 9; Mullis Decl., ¶ 35.)

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
processes, then the T7 RNA polymerase used in Gen-Probe's HIV/HCV test will amplify the sequence attached to the T7 promoter sequence.	
27. The T7 RNA polymerase does not amplify other sequences present in the sample because they are not attached to a T7 promoter sequence.	(Longiaru Decl., ¶ 9; Mullis Decl., ¶35.)
28. Thus, in Gen-Probe's HIV/HCV test, the T7 polymerase enzyme *specifically* recognizes the T7 promoter sequence, which has been *specifically* attached to the target sequence by the binding of *specific* primers, and the T7 polymerase *specifically* amplifies only that sequence.	(Longiaru Decl., ¶ 9; Mullis Decl., ¶ 35.)
29. The process repeats in a cyclic fashion, only amplifying the particular target sequence of interest.	(Longiaru Decl., ¶ 10; Mullis Decl., ¶ 35.)
30. Gen-Probe's amplification method therefore safeguards against amplification of non-target sequences and thus protects against false positive results.	(Longiaru Decl., ¶ 10; Mullis Decl., ¶ 35.)
31. TMA functions in way that is substantially different than the way in which non-specific amplification functions.	(Mullis Decl., ¶ 36.)
32. Specific amplification methods commonly achieve ***exponential*** amplification of the target	(Mullis Decl., ¶ 39.)

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
sequence, as compared with linear amplification.	
33. Sustained, significant, exponential amplification is a hallmark of specific amplification methods.	(Mullis Decl., ¶ 39.)
34. In contrast, the non-specific amplification methods of Examples 4 and 5 of the '338 patent admittedly achieve only linear amplification, not exponential amplification.	(Mullis Decl., ¶ 40.)
35. The non-specific amplification methods of Examples 5 and 6 also cannot achieve exponential amplification. Because random primers bind at various places along the nucleic acids present in the sample, the products of amplification are fragmented.	(Mullis Decl., ¶ 41.)
36. If these products were then subjected to another round of non-specific amplification, the resulting products would be smaller still.	(Mullis Decl., ¶ 40.)
37. Multiple rounds of non-specific amplification thus diminish rapidly in efficiency, whereas multiple rounds of specific amplification produce extraordinarily large amounts of full size product nucleic acids in very short periods of time.	(Mullis Decl., ¶ 40.)
38. Non-specific amplification using random hexamer primers results in fragmented nucleic	(Mullis Decl., ¶ 41.)

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
acids, each of which contains the random sequences present in the primers.	
39. The resulting products are thus heterogeneous and have undefined composition.	(Mullis Decl., ¶ 41.)
40. Such nucleic acids are unsuitable for most of the purposes for which homogeneous, specifically amplified nucleic acids of known composition are employed.	(Mullis Decl., ¶ 41.)
41. As a result, Gen-Probe's TMA method also does not yield the same result as that obtained with non-specific amplification.	(Mullis Decl., ¶ 37-42.)
42. The Court has previously noted that the specification of the '338 patent contains no reference to any specific amplification techniques. To the contrary, the specification clearly suggests that the claimed amplification techniques of the invention don't require the use of specific primers necessary for specific amplification.	See, '338 patent, Exh. 2[2] col. 30, ll. 14-18, col. 30, ll. 30-40.
43. This absence in the '338 patent of any disclosure of specific amplification techniques was not accidental or unintended. To the contrary, Gene-Trak Systems, Vysis' predecessor-in-interest, and its employed	Lawrie Depo., Exh. 3, at 178:19 – 180:11.

[2] Unless otherwise specified, all references to Exhibits shall refer to the exhibits attached to the Notice of Lodgment of Exhibits filed concurrently herewith.

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
inventors were well aware of the specific amplification techniques such as PCR. In fact, the admitted focus of the inventors' effort leading to the disclosure in the '338 patent was to find something "different" from specific amplification. For example, inventor Jon Lawrie testified that the patent was meant to cover *new* amplification methods using non-specific primers, not already-known methods such as PCR: Q. Can you recall any reason that a reference to PCR might have been intentionally omitted from the patent application? A. Yes.... Q. If there's no reference in the ['338] patent to combining target capture with PCR, do you have any explanation as to why it is not there? A. I believe that it was a separate, the thought behind this [referring to the '338 patent] was coming up with *new* methods of amplification, not old ones. Q. For the purposes of what you just said you classify PCR as an old method of amplification? A. PCR itself was described in the patent, issued patent [e.g., it was an "old" method]. Q. And your understanding of the 338 patent was that it was directed to other methods of amplification? A. The, it was, it was directed to	

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
the methods disclosed by, you know, the *methods separate from PCR*.	
44. Inventor King also stated the inventors' purpose and also distinguished non-specific amplification from PCR: Q. From a high level perspective, what were the discussion topics addressed during this meeting? A. I think that at the highest level we were looking for amplification methods ***that did not involve PCR amplification***. (King Depo. At 45:10-15 (emphasis added).) Q. Okay. So the purpose -- the general purpose of the discussion as I understand it that took place at Gene-Trak among the four doctors was to identify -- in general identify an amplification technique that would amplify low concentrations of target nucleic acids in a sample, correct? A. Yes. Q. And as I understand your testimony, you wanted to find a technique ***that was different from PCR***, correct? A. Yes.	King Depo., Exh. 4 at 47:9-20 (emphasis added).
45. As this testimony suggests, PCR was well known to the inventors and the scientific community at large. Dr. Kary Mullis invented PCR in 1983, for which he received the Nobel	Exh. 5 (Saiki *et al.*, "Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia," SCIENCE 230:1350-54 (1985).)

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
Prize in Chemistry. Dr. Mullis and his colleagues publicly described PCR at a scientific meeting in the summer of 1985 and published their discovery in December 20, 1985.	
46. James Richards, Gene Trak's Director of Business Development and Licensing, admits that, within the scientific community, PCR was immediately "big news."	Richards Depo, Exh. 6, at 38:6-8.
47. One of the reasons that the '338 inventors sought to find something "different" from specific amplification techniques such as PCR was due to Gene Trak's concern that it could not obtain a license from Cetus Corp. to use PCR. Cetus Corporation, which employed Dr. Mullis, originally owned the rights to PCR. Gene-Trak sought a license from Cetus, but its requests were rejected.	Richards Depo., Exh. 6, at 66:2-15.
48. This view of the fundamental difference between non-specific and specific amplification techniques was shared not only between the inventors but with Gene-Trak scientific management as well. In particular, in a letter he wrote in 1989, Dr. Richards, pointedly contrasted the '338 patent's method of non-specific amplification with other known specific	Exhibit 7 at page 2, italics added.

UNDISPUTED MATERIAL FACTS:	SUPPORTING EVIDENCE:
methods that used specific primers or promoters: Cetus, Sibia/Salk, Biotechnica, etc. all claim specific primers for amplification *whereas the present invention claims uses of the opposite*, namely, non-specific primer or promoters....	

Dated: October 16, 2001

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